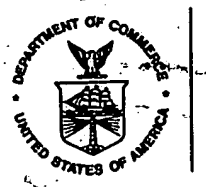

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/492,911	01/27/00	VOGEL	25975-2 JPW

HM11/0214

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EXAMINER	
MITRA,R	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/492,971	VOQEL ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2000 and 19 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

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DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1653.

Status of the Claims

Applicants' preliminary amendments (filed on April 16, 2000 and June 19, 2000) are acknowledged. The Claims 1-87 have been canceled. The amended and new claims 88-96 have been added. Therefore, claims 88-96 are currently pending and are under examination.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 88-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the fibronectin fragments disclosed in the specification, does not reasonably provide enablement for any portion of fibronectin. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 88-96 are directed to an imaging agent which comprises a polypeptide labeled with an imageable marker, wherein such polypeptide has an amino acid sequence which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, wherein the imaging agent is capable of binding to fibrin. The claims are further directed to specific markers including radioactive isotopes, element opaque to x-rays and paramagnetic ions. The specification on page 53 describes three purified polypeptides, having molecular weights of 31 kD, 20 kD and 12 kD derived from the first 262 amino acids of the N-terminal sequence of fibrin binding domain of fibronectin. However, the specification does not define the one fifth portion of the N-terminal sequence nor any correlation between the one fifth portion of sequence with the sequences from where the 31 kD, 20 kD and 12 kD polypeptides are derived. It would require undue experimentation for one of ordinary skill in the art to determine all possible imaging agents derivable, having at least one fifth of the amino acid sequence of the N-terminal region from the fibrin binding domain of fibronectin. A large number of such polypeptides are easily envisioned but the determination of the biological activity of all such polypeptides would require undue experimentation because the purification, refolding and labeling of all such polypeptides is well outside the realm of routine experimental work. One of ordinary skill would require guidance, lacking in the specification, as to exactly what polypeptides might possess the claimed activity. One of ordinary skill would require guidance as to what region of fibronectin is included in the phrase the "fibrin binding domain", what specific amino acids does this encompass, and what is the sequence. It is *a priori* unknown and unpredictable as to which of the large number of polypeptides encompassed by the scope of these claims would have the claimed biological activity i.e. being capable of binding to fibrin. The mere fact that a polypeptide derived from or a fragment of a domain having fibrin binding activity not necessarily would also have fibrin binding activity. Therefore, one of ordinary skill would require guidance in order to make and use of the claimed polypeptides, without such guidance the experimentation left to those skilled in the art is undue.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

Claims 88-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear from the claim 88 or the specification that what is the corresponding amino acid sequence which comprises at least one fifth portion of the amino acid sequence of the N-terminal region of the fibrin binding domain of fibronectin. Is this "one fifth" portion represents a fragment from the upstream or the downstream or in between of that N-terminal region of the fibrin binding domain, however, both the specification and the art lack an unambiguous definition of that term.

Claim 88 is drawn to an agent capable of binding to fibrin. The word "capable" is not clear, since it is not clear whether the agent actually needs to bind the fibrin, or merely have the capability to do so. The word "capable" associates with the latent function only. Amending the claim by deleting the word "capable" would obviate this objection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 88 and 95 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,270,030 in view of Baralle (EP 0 207 751 A1, published on 07.01.87, Bulletin 87/2), Hynes et al. (J. of Cell Biology, Vol. 95, p 369-377, 1982).

Claims 1-8 are directed to an imaging agent composed of a polypeptide labeled with an imageable marker, wherein the polypeptide is a 12 kD polypeptide corresponding to an amino acid sequence present in the fibrin binding domain of naturally- occurring human fibronectin and having the amino acid sequence of amino acids 1-109 and being capable of binding to fibrin (Patent claim 1). The claims of this patent are also directed to a composition comprising an effective amount of the imaging agent and a physiologically acceptable carrier (Patent claim2); the imaging agent wherein the marker is a radioactive isotope, an element opaque to X-rays, or a paramagnetic ion (Patent claim 3; instant application claim 95); the imaging agent wherein the radioactive isotope is indium-111 (Patent claim 5); or technetium-99m (Patent claim 6); the imaging agent wherein the radioactive isotope is iodine-123, iodine-125, iodine-131, krypton-81m, xenon-133 or gallium-67 (Patent claim 7); a purified polypeptide substantially free of other substances of human origin (Patent claim 8). This is the same as instant application claims 88 and 95 which are an obvious variation of patent 5,270,030 claims 1-8. Claim 88 of instant application encompasses the claim 1 of this patent.

The Baralle reference teaches the complete amino acid and nucleic acid sequences of mature human fibronectin (Figure 3). The Baralle reference also teaches that with this disclosure it became possible to provide any desired part of the fibronectin molecule and in particular polypeptides having each of the separate binding activities of fibronectin separate from the others (page 2, lines 33-36). The Baralle reference also teaches that one of the fibronectin binding activities is a fibrin binding activity and that a polypeptide able to bind to fibrin and derived from fibronectin may be used in a therapy to target a therapeutic agent on a natural fibrin e.g. a blood clot (page 5, lines 21-23).

The Hynes reference teaches that the fibronectin polypeptide binds to fibrin via its amino-terminal domain and through site(s) near the carboxyl terminus of the molecule, however, the transglutaminase mediated cross-linking appears to occur only at the amino-terminal domain to a glutamin residue of fibronectin. (page 373, column1: Fibrin and Transglutaminase Interaction sites).

Each of Baralle and Hynes et al. are cited to demonstrate that the amino acid sequence of the fibronectin is known in the art and that the amino terminal fragment of one fifth of the amino acids of the peptide, absent factual data to the contrary would have had a molecular weight of between 12-20 kD.

Claims 88-96 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,121,426 in view of Baralle (EP 0 207 751 A1, published on 07.01.87, Bulletin 87/2), Hynes et al. (J. of Cell Biology, Vol. 95, p 369-377, 1982).

Claims 1-8 are directed to an imaging agent which comprises a polypeptide labeled with an imageable marker, wherein the polypeptide has a molecular weight between about 12 kD and about 20 kD, comprises an amino acid sequence present in the N-terminal fibrin binding domain of naturally-occurring fibronectin, the N-terminal sequence of which is glutamine-alanine-glutamine-glutamine and the length of which is sufficient to encompass the amino acid sequence

of fibronectin required for binding to fibrin, and wherein the imaging agent is capable of binding to fibrin and wherein the marker is selected from the group consisting of indium-111, technetium-99m, iodine-123, iodine-131, krypton-81m, xenon-133, gallium-67 and paramagnetic ions. The claims of this patent are also directed to a method for imaging a fibrin containing substance which comprises contacting the fibrin –containing substance with the imaging agent under conditions such that the imaging agent binds to fibrin in the fibrin containing substance, detecting the presence of any of imaging agent bound to fibrin and thereby imaging the fibrin-containing substance (Patent claim 2; instant application claim 89); the method of claim 2, wherein the fibrin- containing substance is a thrombus (Patent claim 3; instant application claim 90); the method of claim 2 wherein the fibrin-containing substance is atherosclerotic plaque (Patent claim 4; instant application claim 91); the method of claim 2 wherein the fibrin-containing substance is within blood vessels of a subject and wherein contacting is performed by administering the imaging agent contained in a suitable carrier to the subject under conditions permitting the imaging agent to enter the blood vessels of the subject (Patent claim 5; instant application claim 92); the method of claim 5, wherein the fibrin-containing substance is a thrombus (Patent claim 6; instant application claim 93); the method of claim 5, wherein the fibrin-containing substance is atherosclerotic plaque (Patent claim 7; instant application claim 94); the method of claim 2 wherein the imaging is carried out using a gamma camera (Patent claim 8; instant application claim 96). These claims are directed to the same materials and methods of the instant application claims and thus, the instant application claims are an obvious variation of the patented claims 1-8 of the 6,121,426. Claim 88 of instant application encompasses the claim 1 of this patent.

The Baralle reference teaches the complete amino acid and nucleic acid sequences of mature human fibronectin (Figure 3). The Baralle reference also teaches that with this disclosure it became possible to provide any desired part of the fibronectin molecule and in particular polypeptides having each of the separate binding activities of fibronectin separate from the others (page 2, lines 33-36). The Baralle reference also teaches that one of the fibronectin binding activities is a fibrin binding activity and that a polypeptide able to bind to fibrin and derived from fibronectin may be used in a therapy to target a therapeutic agent on a natural fibrin e.g. a blood clot (page 5, lines 21-23).

The Hynes reference teaches that the fibronectin polypeptide binds to fibrin via its amino-terminal domain and through site(s) near the carboxyl terminus of the molecule, however, the transglutaminase mediated cross-linking appears to occur only at the amino-terminal domain to a glutamin residue of fibronectin. (page 373, column1: Fibrin and Transglutaminase Interaction sites).

Each of Baralle and Hynes et al. are cited to demonstrate that the amino acid sequence of the fibronectin is known in the art and that the amino terminal fragment of one fifth of the amino acids of the peptide, absent factual data to the contrary would have had a molecular weight of between 12-20 kD.

Claims 88-96 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,965,383 in view of Baralle (EP 0 207 751 A1, published on 07.01.87, Bulletin 87/2), Hynes et al. (J. of Cell Biology, Vol. 95, p 369-377, 1982).

Claims 1-21 of the 5,965,383 patent are directed to an imaging agent which comprises a polypeptide labeled with an imageable marker, wherein the polypeptide has a molecular weight between about 12 kD and about 20 kD and an amino acid sequence substantially the same as an amino acid sequence present in the fibrin binding domain of naturally-occurring fibronectin, and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide and wherein the imaging agent is capable of binding to fibrin. The imaging agent of claim 1, wherein the marker is a radioactive isotope, an element which is opaque to X-rays, or a paramagnetic ion (Patent claim 3). The claims of this patent are also directed to a method for imaging a fibrin containing substance which comprises contacting the fibrin containing substance with the imaging agent of claim 1 under conditions such that the imaging agent binds to fibrin in the fibrin containing substance, detecting the presence of any of imaging agent bound to fibrin and thereby imaging the fibrin-containing substance (Patent claim 14; instant application claim 89); the method of claim 14, wherein the fibrin- containing substance is a thrombus (Patent claim 15; instant application claim 90); the method of claim 14, wherein the

fibrin-containing substance is atherosclerotic plaque (Patent claim 16; instant application claim 91); the method of claim 14, wherein the fibrin-containing substance is within blood vessels of a subject and wherein contacting is performed by administering the imaging agent contained in a suitable carrier to the subject under conditions permitting the imaging agent to enter the blood vessels of the subject (Patent claim 17; instant application claim 92); the method of claim 17, wherein the fibrin-containing substance is a thrombus (Patent claim 18; instant application claim 93); the method of claim 17, wherein the fibrin-containing substance is atherosclerotic plaque (Patent claim 19; instant application claim 94); the imaging agent of claim 14, wherein the marker is a radioactive isotope, an element opaque to X-rays, or a paramagnetic ion (Patent claim 20; instant application claim 95); the method of claim 14 wherein the imaging is carried out using a gamma camera (Patent claim 21; instant application claim 96). This is the same as instant application claims 88-96 which are an obvious variation of the patented claims of 1-21 of Patent 5,965,383. Claim 88 of instant application encompasses the claim 1 of this patent.

The Baralle reference teaches the complete amino acid and nucleic acid sequences of mature human fibronectin (Figure 3). The Baralle reference also teaches that with this disclosure it became possible to provide any desired part of the fibronectin molecule and in particular polypeptides having each of the separate binding activities of fibronectin separate from the others (page 2, lines 33-36). The Baralle reference also teaches that one of the fibronectin binding activities is a fibrin binding activity and that a polypeptide able to bind to fibrin and derived from fibronectin may be used in a therapy to target a therapeutic agent on a natural fibrin e.g. a blood clot (page 5, lines 21-23).

The Hynes reference teaches that the fibronectin polypeptide binds to fibrin via its amino-terminal domain and through site(s) near the carboxyl terminus of the molecule, however, the transglutaminase mediated cross-linking appears to occur only at the amino-terminal domain to a glutamin residue of fibronectin. (page 373, column1: Fibrin and Transglutaminase Interaction sites).

Each of Baralle and Hynes et al. are cited to demonstrate that the amino acid sequence of the fibronectin is known in the art and that the amino terminal fragment of one fifth of the amino

acids of the peptide, absent factual data to the contrary would have had a molecular weight of between 12-20 kD.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use the claims of the patents 6,121,426, 5,965,383 and 5,270,030 in combination with the teachings of Baralle, F. E. and Hynes et al. to arrive at an imaging agent which comprises a polypeptide labeled with an imageable marker, such polypeptide having an amino acid sequence which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, which was capable of binding to fibrin. One skilled in the art would have been motivated to pursue a fragment of such imaging agent because of the demonstrated binding activity of the amino acid sequence identical to an amino acid sequence present in the N-terminal sequence of fibrin binding domain of fibronectin the N-terminal sequence of which is glutamine-alanin-glutamin-glutamin (patent 6,121,426), or met-gln-ala-gln-gln (patent 5,965,383). Therefore, the claims are obvious over the cited references and the claims of the patents 6,121,426, 5,965,383 and 5,270,030.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rita Mitra, Ph.D.
December 24, 2000

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